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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,702	11/21/2003	Tomoyuki Tokunaga	3462.1007-000	1351

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EXAMINER	
HAMA, JOANNE	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/719,702	TOKUNAGA ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant filed a response to the Non-Final Rejection of March 1, 2006 on September 1, 2006. Claims 7-34 are cancelled. Claims 1-6 are amended.

Claims 1-6 are under consideration.

Information Disclosure Statement

Applicant filed an IDS on September 1, 2006. The IDS has been considered. Applicant indicates that on the copy of the form PTO-1449, the Examiner crossed out reference AR (Furusawa, T et al., 2002) and wrote, "Not present." Applicant indicates that reference AR was submitted with PTO-1449 on April 23, 2004 (Applicant's response, September 1, 2006, page 5). In response, the Examiner acknowledges that reference AR, file April 23, 2004, has been received and considered.

Withdrawn Rejections

35 U.S.C. § 102(b)

Applicant's arguments, see pages 10-11 of Applicant's response, filed September 1, 2006, with respect to the rejection of claims 1-3 have been fully considered and are persuasive. Applicant indicates that claim 1 has been amended to recite a method of isolating undifferentiated cells that primarily differentiate into an epiblast. The method comprises a step of selecting for undifferentiated cells that express PECAM-1 on their surface. Applicant indicates that Thomson does not teach the isolation of undifferentiated cells that primarily differentiate into an epiblast of a

blastocyst, nor does Thomson teach the isolation of these undifferentiated cells by sorting them through the expression of PECAM-1 (Applicant's response, page 11, 1st parag.). The rejection of claims 1-3 has been withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 remain rejected in modified form under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record, March 1, 2006.

Applicant's amendments to the claims raise new issues of enablement and are discussed as follows. Response to Applicant's rebuttals, filed September 1, 2006, follows the new issues of enablement.

Claim 1 has been amended to more specifically claim a method of isolating undifferentiated cells by identifying and collecting undifferentiated cells that express PECAM-1 on the cell surface. That is, the claim has been interpreted as: the only cell surface marker that would need to be used to identify any undifferentiated cell (from any species of animal) that has the ability to differentiate into an epiblast of a blastocyst is

PECAM-1. As claim 1 encompasses this embodiment, the specification does not provide guidance to arrive at the invention as claimed. Further, the limitation of claim 2, wherein claim 2 indicates that the population of undifferentiated cells expresses SSEA-1, does not provide guidance for an artisan to arrive at any undifferentiated cells that primarily differentiate into an epiblast.

At the time of filing, the specification teaches that undifferentiated cells are selected using cell-surface antigens as indicators. Generally, this can be achieved by contacting antibodies to their cell-surface antigens. The specification indicates that cell-surface antigens are selected from the group consisting of PECAM-1, SSEA-1, SSEA-3, and SSEA-4 (specification, page 6, 1st parag. under "Detailed Description of the Invention"). While the specification teaches that these markers can be used to identify undifferentiated cells, the art teaches that using PECAM-1 and SSEA-1 (the markers used in the claims) to identify undifferentiated ES cells is not sufficient. According to the art, after growing for 6 days in differentiation medium, ES cells are PECAM positive and grow in clumps or cords and are distinguished from mature blood island endothelial cells by lack of expression of CD34 and are not distinguished from ES cells by the other marker used in the study (Redick and Bautch, 1999, American Journal of Pathology, 154: 1137-1147, page 1143, 2nd col., 1st parag. under "ES Colony Recovery from Differentiating Cultures"). The other marker used in the study is SSEA-1 (Redick and Bautch, page 1138, 2nd col., 1st parag. under "Immunolocalization"). As such, Redick and Bautch's study indicates that using the marker SSEA-1 is not sufficient in discriminating undifferentiated cells from endothelial cells. To further illustrate this point,

one of the conclusions in their study was, "(u)ndifferentiated ES cells express PECAM, and we confirmed this finding using double immunofluorescence analysis with PECAM and SSEA-1, a marker of undifferentiated and partially differentiated embryonic cells (Redick and Bautch, page 1145, 2nd col., 2nd parag.)". As such, that a cell expresses PECAM and SSEA-1 is not indicative that the cell is undifferentiated.

Thus, the claims are rejected.

Response to Arguments

Applicant's arguments, pages 5-10, filed September 1, 2006 have been fully considered but they are not persuasive.

With regard to the issue of the use of markers used to identify undifferentiated cells, Applicant indicates that claim 1 has been amended to recite, "sorting the population of undifferentiated cells according to presence or absence of PECAM-1 on the surface of said cells (Applicant's response, page 7, 1st parag.)." In response, Applicant's amendment is not persuasive because the specification does not provide guidance for an artisan to identify undifferentiated cells from different species of animals, as encompassed in claim 1. As a first matter, as indicated above, the art (Redick and Bautch) teaches that an artisan cannot reasonably predict that cells expressing PECAM-1 and SSEA-1 are undifferentiated. With regard to Applicant indicating that the art (Levenberg et al., 2002, provided by Applicant) teaches support that human ES cells express PECAM-1 (Applicant's response, page 7, 1st parag.), this argument is not found persuasive. This is because Levenberg et al. teach that human ES cells do not express PECAM-1 (see Levenberg, et al., Figure 1, where RT-PCR

results indicate that human ES cells do not express PECAM-1). With regard to Applicant indicating that Thomson (U.S. Paten 5,843,780) is silent regarding the expression PECAM-1 on the surface of primate or mouse ES cells (Applicant's response, page 6, 1st parag. under "ES Cell Marker Expression"), nothing in the specification or in Thomson teaches that human cells express PECAM-1 such that undifferentiated human ES cells can be identified. An artisan cannot reasonably predict that cells across different species of animals can necessarily be defined by the same cell surface markers. This was illustrated by Thomson, Table 1. Note that mouse ES cells express SSEA-1 and monkey ES cells and human EC cells do not; note also that monkey ES cells and human EC cells express SSEA-3, SSEA-4, Tra-1-60, Tra-1-81, whereas mouse ES cells do not. As such, Thomson's teachings indicate that an artisan cannot reasonably predict that cell surface marker expression is conserved between different species of animals and that cell surface markers can be used to identify population of cells amongst different species of animals. As such, with regard to claim 1 encompassing a broad scope of cells from different species of animals, the amendment is not persuasive and thus the rejection is maintained.

Regarding the issue of ES cell derivation and use (Applicant's response, pages 8-10), Applicant indicates that ES cells can be obtained from many different mammalian species, including mouse, rat, rabbit, and humans (Applicant's response, page 8, 1st parag., under "ES Cell Derivation and Use"). Applicant indicates that the technology to achieve germline transmission of ES cells from animals other than mouse was not well-established, is irrelevant to the claimed invention. In response, this is not persuasive.

The fact that no animal ES cell, other than mouse, can achieve germline transmission is germane to the issue of enablement because it is one of the characteristics of an ES cell. Thus, because the art teaches that mouse is the only species of animal that has demonstrated germline transmission the scope of the claims is limited to mouse. Applicant indicates that ES cells from other species of animals have been used in other applications, such as regenerative medicine to grow tissues, skin, or other cells for transplantation in a patient (Applicant's response, page 9, 1st parag.). In response, this is not persuasive because teaching that ES cells from other species of animals can be used in other applications does not address that ES cells, other than that of mouse, achieve germline transmission. As such, the rejection of the claims as they apply to this issue is maintained.

Thus, the claims remain rejected.

It is noted that the rejection of claim 7 is withdrawn as claim 7 is cancelled.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5, 6 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Redick and Bautch, 1999, American Journal of Pathology, 154: 1137-1147.

Redick and Bautch teach that mouse embryonic stem (ES) cells were examined for expression of PCAM and SSEA-1 via antibody detection (Redick and Bautch, page 1139, 2nd col. under "PECAM Expression in ES cells" to page 1140, 1st col., 1st parag.). Redick and Bautch teach that PECAM and SSEA-1 expressed in undifferentiated cells (Redick and Bautch, page 1137, 2nd col., 2nd parag., and page 1140, 1st col., 1st parag.).

While Redick and Bautch do not specifically teach that the mouse ES cells selected for PECAM-1 expression differentiate into an epiblast of a blastocyst, the ability for the mouse ES cells of Redick and Bautch to do so would have been inherent. It is noted that the specification teaches the steps of identifying mouse ES cells using antibody staining and teaches that PECAM+ SSEA-1+ mouse ES cells injected into ICR mouse embryos resulted in a high percentage of PECAM-1 positive cells were incorporated into the epiblast (specification, Example 5 and Figure 6). Because the method of treatment was the same between the specification and Redick and Bautch (i.e., the selection of ES cells based on protein expression, detected by antibodies), the ES cells of Redick and Bautch would have been the same as that described in the specification.

Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden

of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Thus, Redick and Bautch anticipate claims 1-3, 5, 6.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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JH

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PRIMARY EXAMINER